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Sources of toxicity and exposure information for identifying chemicals of high concern to children

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ABSTRACT

Due to the large number of chemicals in commerce without adequate toxicity characterization data, coupled with an ineffective federal policy for chemical management in the United States, many states are grappling with the challenge to identify toxic chemicals that may pose a risk to human health and the environment. Specific populations (e.g., children, elderly) are particularly sensitive to these toxic chemicals. In 2008, the Children's Safe Product Act (CSPA) was passed in Washington State. The CSPA included specific requirements to identify High Priority Chemicals (HPCs) and Chemicals of High Concern to Children (CHCCs). To implement this legislation, a methodology was developed to identify HPCs from authoritative scientific and regulatory sources on the basis of toxicity criteria. Another set of chemicals of concern was then identified from authoritative sources, based on their potential exposure to children. Exposure potential was evaluated by identifying chemicals detected in biomonitoring studies (i.e., human tissues), as well as those present in residential exposure media (e.g., indoor air, house dust, drinking water, consumer products). Accordingly, CHCCs were defined as HPCs that also appear in biomonitoring studies or relevant exposure media. For chemicals with unique Chemical Abstracts Service (CAS) numbers, we identified 2044 HPCs and 2219 chemicals with potential exposure to children, resulting in 476 CHCCs. The process of chemical identification is dynamic, so that chemicals may be added or subtracted as new information becomes available. Although beyond the scope of this paper, the 476 CHCCs will be prioritized in a more detailed assessment, based on the strength and weight of evidence of toxicity and exposure data. Our approach was developed to be flexible which allows the addition or removal of specific sources of toxicity or exposure information, as well as transparent to allow clear identification of inputs. Although the methodology was constrained by specific requirements in the CSPA, the intent of this work was to identify HPCs and CHCCs that might guide future regulatory actions and inform chemical management policies, aimed at protecting children's health.

1. Introduction

With over 100,000 chemicals in commercial use (Snyder et al., 2000; Judson et al., 2009) along with ineffective regulations and mounting public concerns, chemical policy in the United States (US) is ripe for reform. Governmental agencies in the European Union and several US states have recently passed legislation to increase their control over toxic chemicals (Service, 2009). Some of this legislation has been directed toward protection of children, based on growing research linking adverse health effects in children with exposure to environmental chemicals (USEPA, 2006, 2008a; WHO, 2006).

In 2008, the Washington State legislature passed into law the Children's Safe Product Act (CSPA). The CSPA directed the Washington State Department of Ecology (WDOE) to identify High Priority Chemicals (HPCs) and Chemicals of High Concern to Children (CHCCs) (WSL, 2008). The legislation was in response to public concern related to chemical use and the potential risk these chemical pose to sensitive populations (Grandjean et al., 2007). During the previous 2 years, millions of toys were recalled due to excessive levels of lead (WDOE, 2008a). In addition, concerns were raised about other chemicals (e.g., phthalates, bisphenol A) found in consumer products marketed to children (CCS, 2009).

Similar legislation has been passed in other states, including Maine, Connecticut, Minnesota, Michigan, Massachusetts, and California. As in Washington State, the legislation in Maine, Minnesota, and Connecticut is primarily focused on the impact of chemicals on children's health. Legislation in California, Michigan, and Massachusetts is more broadly based, directed toward developing a more comprehensive chemical management policy.

Washington's CSPA included specific criteria on toxicity and potential exposure to be used to identify those chemicals that pose a risk to children. As such, the initial step in the methodology was to compile a list of HPCs from authoritative scientific and regulatory sources. These sources included toxicity information relevant to both

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children and adults. Another set of chemicals was then identified from authoritative sources, based on their detection in biomonitoring studies (e.g., blood, urine, breast milk, etc.), as well as their presence in residential exposure media (e.g., indoor air, house dust, drinking water, consumer products). Although this exposure assessment omits key pathways exempted by the CSPA (e.g., food consumption), it nonetheless evaluates relevant criteria. This information on exposure potential was aimed primarily at children. Those HPCs with a potential for exposure to children defined our inventory of CHCCs. In this context, the purpose of our study was to identify HPCs and CHCCs that might then guide future regulatory actions (e.g., reporting and tracking requirements) and inform chemical management policies.

It is hoped that the methodology described in our study may prove useful to other regulatory agencies, tasked with similar issues, concerning chemical use and potential risk to sensitive populations. The process of identifying chemicals of concern needs to guard against false negatives that may contribute to human health and environmental problems, as well as false positives that may cause socioeconomic harm (Klecka and Muir, 2008). Our methodology is intended to be both flexible and transparent. Because compiling a list of chemicals of concern is a dynamic process, flexibility allows information to be updated periodically, as more data become available. For example, it was important to establish a process that captures emerging chemicals of concern (e.g., nanomaterials, pharmaceuticals, personal care products, flame retardants), as well as chemicals with a more complete toxicity database. In addition, the process must be transparent, so that interested parties can trace and replicate our methodology.

2. HPCs and CHCCs as defined in CSPA

HPCs are defined in the CSPA as follows: "a chemical identified by a state agency, federal agency, or accredited research university, or other scientific evidence deemed authoritative by the department [WDOE] on the basis of credible scientific evidence as known to do one or more of the following: (a) harm the normal development of a fetus or child or cause other developmental toxicity; (b) cause cancer, genetic damage, or reproductive harm; (c) disrupt the endocrine system; (d) damage the nervous system, immune system, or organs or cause other systemic toxicity; (e) be persistent, bioaccumulative, and toxic; or (f) be very persistent and very bioaccumulative."

Once HPCs have been identified, the CSPA directs WDOE to identify CHCCs: "the department [WDOE].....shall identify high priority chemicals that are of high concern for children after considering a child's or developing fetus's potential for exposure to each chemical. In identifying the chemicals, the department shall include chemicals that meet one or more of the following criteria: (a) the chemical has been found through biomonitoring studies that demonstrate the presence of the chemical in human umbilical cord blood, human breast milk, human urine, or other bodily tissues or fluids; (b) the chemical has been found through sampling and analysis to be present in house dust, indoor air, drinking water, or elsewhere in the home environment; or (c) the chemical has been added to or is present in a consumer product used or present in the home."

3. Sources of toxicity information

Numerous authoritative scientific and regulatory sources of toxicity information were reviewed to identify HPCs. In addition, we coordinated with other states that have similar legislation in order to reach agreement on the universe of HPCs. Although there was incomplete agreement among states, due to differences in their respective legislation and input from their advisory committees, the basic methodology was similar. Authoritative scientific and regulatory sources of toxicity information, used in our study, are listed in Table 1.

Table 1
Authoritative scientific and regulatory sources used to identify High Priority Chemicals (HPCs).

Country/ organization	Source[a]
United States (Federal)	EPA Voluntary Children's Chemical Exposure Program (VCCEP)
	EPA Toxics Release Inventory (TRI) Program
	EPA Integrated Risk Information System (IRIS)
	EPA National Waste Minimization Program (NWMP)
	NTP Center for the Evaluation of Risks to Human Reproduction (CERHR)
	NTP Report on Carcinogens (RoC)
United States (State)	California Proposition 65 Program (Prop 65)
	Washington (WA) Persistent, Bioaccumulative, and Toxic (PBT) Program
Canada	Canadian Environmental Protection Act (CEPA)
European Union (EU)	Substances of Very High Concern (SVHC)
	Endocrine Disruptor (ED) Program
	PBT Program
	Existing Substances Regulation (ESR)
Other	International Agency for Research of Cancer (IARC)
	Oslo–Paris Commission (OSPAR)
	Grandjean and Landrigan (2006)

[a] EPA = Environmental Protection Agency; NTP = National Toxicology Program.

A short description of each source is provided, along with internet links in the Reference list for more detailed information.

3.1. US Environmental Protection Agency (EPA)

EPA is the primary federal agency charged with protecting the environment. As part of its mission, EPA has established programs and tools to work with businesses to address problems that impact their mission. Four EPA programs or tools that have identified chemicals of concern were reviewed, and these chemicals were included in the list of HPCs.

3.1.1. Voluntary Children's Chemical Exposure Program (VCCEP)

In support of its mission to protect human health, EPA established the VCCEP (USEPA, 2008b). VCCEP identifies chemicals that have a potential impact on the health of children and for which sufficient toxicity information is available to quantify their risks (USEPA, 2008c). EPA has asked that manufacturers of these chemicals voluntarily provide additional information on toxicity and risk. VCCEP chemicals are identified in column "EPA_VCCEP" in Table S1. Table S1 is published online as supplementary material (Excel file) and includes chemical name, Chemical Abstracts Service (CAS) registry number (when available), and toxicity information source.

3.1.2. Toxics Release Inventory (TRI) Program

EPA is charged with implementing the Emergency Planning and Community Right to Know Act (EPCRA). EPCRA requires businesses and other organizations to report chemical releases to the environment. Toward this aim, EPA maintains the TRI, a database that summarizes releases of toxic chemicals reported to EPA (USEPA, 2008d).

In 1999, EPA established TRI reporting requirements for a list of persistent, bioaccumulative, and toxic (PBT) chemicals (USEPA, 2008e,f). These PBTs were identified, because these chemicals "were found to be reasonably anticipated to cause serious or irreversible chronic human health effects at relatively low doses or ecotoxicity at relatively low concentrations, and thus are considered to have moderately high to high chronic toxicity or high ecotoxicity" (FR, 1999). In this process, EPA identified several individual PBT chemicals, as well as chemical categories (e.g., dioxin and dioxin-like compounds, mercury compounds, lead compounds, polycyclic aromatic

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hydrocarbons [PAHs]). TRI chemicals are identified in column "EPA_TRI" in Table S1.

3.1.3. Integrated Risk Information System (IRIS)

EPA states on its website, "IRIS is a compilation of electronic reports on specific substances found in the environment and their potential to cause human health effects. IRIS was initially developed for EPA staff in response to a growing demand for consistent information on substances for use in risk assessments, decision-making, and regulatory activities. The information in IRIS is intended for those without extensive training in toxicology, but with some knowledge of health sciences" (USEPA, 2008g).

The IRIS database currently contains information on 548 chemicals or groups of chemicals. This database can be searched to determine chemicals of concern, due to specific toxicity criteria. For example, IRIS was searched for human carcinogens using the Advanced Search function provided by EPA (USEPA, 2008h). Data from the following were selected for inclusion: 1986 Guidelines (Category A—known, B—probable, C—possible human carcinogens), 1996 Guidelines (known and likely human carcinogens), 1999 Guidelines (known and likely carcinogens), 2005 guidelines (known and likely carcinogens), as well as remaining chemicals in IRIS (primarily with non-cancer effects). Although this latter category may contain several chemicals which lack documented toxicity, these chemicals can be eliminated in subsequent iterations of our methodology. IRIS chemicals are identified in seven columns (IRIS_86A, IRIS_86B, IRIS_86C, IRIS_96, IRIS_99, IRIS_05, IRIS_OTHER) in Table S1.

3.1.4. National Waste Minimization Program (NWMP)

EPA established the NWMP to promote a more sustainable society by reducing the amount of waste generated and lowering the toxicity and persistence of wastes that are generated (USEPA, 2008i). The NWMP established a list of priority chemicals that consists of 28 "organic chemicals and chemical compounds" and three "metals and metal compounds" (USEPA, 2008j). EPA is assisting businesses to remove these priority chemicals from manufacturing processes and products and to identify safer alternatives. NWMP chemicals are identified in column "EPA_NWMP" in Table S1.

3.2. US-National Toxicology Program (NTP)

The NTP is an interagency program managed by the US Department of Health and Human Services (DHHS) whose mission is to evaluate agents of public health concern by developing and applying tools of toxicology and molecular biology. The need for a program like NTP arose because of increasing scientific, regulatory, and Congressional concerns about the human health effects of chemical agents in our environment (USDHHS, 2008a). The NTP has identified chemicals that pose a threat to human reproduction and are known or suspected carcinogens. Two NTP programs are reviewed below.

3.2.1. Center for the Evaluation of Risks to Human Reproduction (CERHR)

The NTP CERHR was established in 1998 to serve as an environmental health resource to the public and regulatory and health agencies. CERHR publishes monographs that assess evidence that environmental chemicals, physical substances, or mixtures cause adverse effects on reproduction and development (USDHHS, 2008b). Through this process, CERHR has identified several chemicals of concern (USDHHS, 2008c). CERHR chemicals are identified in column "NTP_CERHR" in Table S1.

3.2.2. Report on Carcinogens (RoC)

The NTP also publishes a list of carcinogens in its RoC. The RoC is a scientific and public health document first ordered by Congress in 1978 that identifies and discusses agents, substances, mixtures, or exposure circumstances that may pose a hazard to human health, due to their carcinogenicity (USDHHS, 2008d). The RoC includes two categories of carcinogenic compounds, chemicals known to be human carcinogens (Category A) and chemicals reasonably anticipated to be human carcinogens (Category B). RoC chemicals are identified in two columns as known (NTP_CatA) and reasonably anticipated (NTP_CatB) carcinogens in Table S1.

3.3. US states

Several states have passed legislation that addresses environmental chemicals of concern (e.g., California, Washington State). These programs include specific information that may prove useful with future strategies for chemical prioritization. For example, the California program specifies "no significant risk levels" (NSRLs) for carcinogens and "maximum allowable daily levels" (MADLs) for reproductive toxicants. Although the NSRL and MADL values are not used during this process, these may prove useful in future chemical prioritization steps or in the development of de minimis values for reporting requirements.

3.3.1. California's Proposition 65 Program

Proposition 65 (Prop 65), the Safe Drinking Water and Toxic Enforcement Act of 1986, was enacted as a Californian ballot initiative in 1986. Prop 65 was intended to protect California citizens and the state's drinking water resources from chemicals known to cause cancer, birth defects, or other reproductive harm, and to inform citizens about exposures to such chemicals (CalEPA, 2008a). Each year, the Office of Environment Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency (CalEPA) publishes an updated list of chemicals of concern (CalEPA, 2008b). Prop 65 chemicals are identified as having any or all of four major toxicity concerns including 1) carcinogenicity, 2) reproductive toxicity, 3) impacts on male development, or 4) impacts on female development. Chemicals identified for each concern are listed in separate columns (Prop65_CAR, Prop65_REP, Prop65_MAL and Prop65_FEM) in Table S1.

3.3.2. Washington State PBT Program

In 2006, WDOE adopted regulations specific to PBTs (WDOE, 2008b). Explicit criteria were established for persistence, bioaccumulation, and toxicity. The legislation requires WDOE to issue one Chemical Action Plan (CAP) each year, until all of the PBTs are assessed. In addition, WDOE is required to prioritize PBTs and to address first those that pose the greatest threat to human health and the environment (WDOE, 2008c). WDOE PBTs are identified in column "WA_PBT" in Table S1.

3.4. Canada

The Canadian Environmental Protection Act (CEPA) is Canada's federal environmental legislation, aimed at preventing pollution and protecting human health and the environment (CEPA, 2008a). As part of this effort, the Canadian government established a list of chemicals imported to or produced in Canada, known as the Domestic Substances List (DSL). Chemicals on the DSL have been prioritized, using a wide range of toxicity criteria, and results are available on the web (CEPA, 2008b). Only persistent, bioaccumulative, and inherently toxic (PB_iT) chemicals were included in our HPC list. Canadian PB_iTs are identified in column "CAN_PB_iT" in Table S1.

3.5. European Union (EU)

3.5.1. Substances of Very High Concern (SVHC) Program

The European Chemicals Agency (ECHA) prepares Annex XV dossiers for identification of SVHCs, defined in the Registration, Authorization, and Restriction of Chemical Substances (REACH) regulation. SVHCs include PBTs or very persistent and very bioaccumulative (vPvB) chemicals, along with substances that are carcinogenic, mutagenic, or reproductive (CMR) toxicants or that cause serious effects to

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human health or the environment at an equivalent level of concern as PBTs, vPvBs, or CMRs (e.g. endocrine disrupters) (ECHA, 2008). SVHCs are identified in column "EU_SVHC" in Table S1.

3.5.2. Endocrine Disruptor Program

The mission of the European Commission (EC) is to promote the general interest of the EU. As such, the EC presents proposals for European law by overseeing the correct implementation of Treaties and European law, carrying out common policies, and managing funds (EC, 2008a). The EC conducts work on a wide range of environmental issues and has established several databases which address chemical safety. In 1999, the EC adopted, "Communication on a Community Strategy for Endocrine Disrupters," focusing on substances suspected of interfering with hormone systems in humans and wildlife. The communication addresses exogenous substances (e.g., natural or synthetic) that may harm health, causing cancer, behavioral changes, and reproductive abnormalities (EC, 2008b).

According to the strategy, endocrine disruptors have been grouped into four major categories: Category 1 (evidence of endocrine disruption activity), Category 2 (some in vitro evidence of biological activity related to endocrine disruption), Category 3A (no data available on wildlife relevant and/or mammal relevant endocrine effects), and Category 3B (some data available but evidence is insufficient for identification). The EC provides a database that contains all of the chemicals reviewed and allows segregation of chemicals into the above categories (EC, 2008c). Only chemicals in Categories 1 (EU_END1) and 2 (EU_END2) were included in our HPC list (Table S1).

3.5.3. PBT Program

In June 2001, the EC initiated an interim strategy to address PBT chemicals. Results of this work can be found in their internet database, European Chemical Substances Information System (ESIS), which identifies PBT or vPvB chemicals (EC, 2008d). These were added to our HPC list and are identified in column "EU_PBT" in Table S1.

3.5.4. Existing Substances Regulation (ESR)

The EC also maintains a website providing information to address ESR that requires a comprehensive framework for evaluation and control of "existing substances." ESR states, "The EC, in consultation with Member States, will regularly draw up sources of priority substances which require immediate attention because of their potential impacts on man or the environment" (EC, 2008e). Due to their potential impact upon human health and the environment, ESR chemicals were included in our HPC list and appear in column "EC_ESR" in Table S1.

3.6. Other

3.6.1. International Agency for Research on Cancer (IARC)

IARC is part of the World Health Organization (WHO) of the United Nations. IARC's mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships (WHO, 2008a).

IARC publishes monographs that identify carcinogenic chemicals and assigns them to the following groups: Group 1 (carcinogenic to humans), Group 2A (probably carcinogenic to humans), Group 2B (possibly carcinogenic to humans), Group 3 (not classifiable as to its carcinogenicity to humans), and Group 4 (probably not carcinogenic to humans) (WHO, 2008b). Chemicals in Groups 1 (IARC_1), 2A (IARC_2A), and 2B (IARC_2B) were added to our HPC list (Table S1).

3.6.2. Oslo–Paris Commission (OSPAR)

OSPAR was originally formed in 1972 to control dumping of waste into the North Sea. The commission is a consortium of 15 European countries and the European Community whose mission is to protect the marine environment of the North-East Atlantic. OSPAR has expanded over the years to include land based and production sources of potential pollution to the North-East Atlantic. The 1992 OSPAR Convention is the current instrument guiding international cooperation to meet these objectives (OSPAR, 2008a).

OSPAR has conducted research to identify chemicals of concern to the North-East Atlantic region. The first set of chemicals or chemical groups consists mainly of PBTs, along with a few endocrine disruptors (OSPAR, 2008b), and is identified by OSPAR as "chemicals of concern". In addition, OSPAR is focusing on a second, smaller group of chemicals for priority action (OSPAR, 2008c). Both chemicals of concern (OSPAR_COC) and chemicals for priority action (OSPAR_PA) are found in separate columns in Table S1.

3.6.3. Grandjean and Landrigan (2006)

Grandjean and Landrigan (2006) reviewed developmental neurotoxicity of industrial chemicals to highlight the vulnerability of the developing nervous system. These researchers identified 201 potential neurotoxins, based upon information from the IRIS database, the Hazardous Substances Database (HSDB), and data provided by the US Agency for Toxic Substances and Disease Registry (ATSDR). However, we found two CAS entries in HSDB for one of their neurotoxins, representing two isomers of the pesticide, "chlorthion." Because we included both of these CAS numbers, we added 202 chemicals from this source to our HPC list. This illustrates one of the challenges associated with chemical identification. These potential neurotoxins are found in column "GL_NEU" in Table S1.

4. Compilation of HPCs and sources of toxicity information

Primary toxicity criteria and toxicity information sources are summarized for HPCs in Table 2. Numbers of HPCs in this table represent a compilation before removal of multiple listings. A more detailed

Table 2
Primary toxicity criteria and information sources for High Priority Chemicals (HPCs).

Primary toxicity criteria[a]	Source of information[b]	Number of HPCs
Carcinogenicity	Prop 65	446
	NWMP	8
	IARC	321
	IRIS	138
	NTP	238
DNR toxicity	Prop 65	414
	VCCEP	23
	Grandjean and Landrigan (2006)	202
	NTP	39
CMR toxicity	NWMP	20
	ESR	141
	SVHC	10
Endocrine disruption	EU ED	317
	OSPAR	22
PBT	CEPA PB$_i$T	393
	TRI	72
	NWMP	5
	EU PBT	61
	SVHC	5
	OSPAR	336
	WA PBT	75
vPvB	SVHC	1
Other	IRIS	423
		3710 total (sum)
		2160 unique (sum)
		2044 unique (CAS)[c]

[a] DNR = Developmental, Neurological, or Reproductive; CMR = Carcinogenic, Mutagenic, or Reproductive; PBT = Persistent, Bioaccumulative, and Toxic; vPvB = Very Persistent and Very Bioaccumulative.

[b] See Table 1 for abbreviations; PB$_i$T = Persistent, Bioaccumulative, and inherently Toxic.

[c] CAS = Chemical Abstracts Service registry number.

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compilation of HPCs can be found in Table S1. In addition to toxicity source information, Table S1 presents a quantitative summary of total chemical entries with and without CAS numbers, as well as unique chemicals with and without unique CAS numbers.

CAS numbers were identified for each chemical to detect multiple listings, which appeared as a result of accessing multiple information sources or due to the use of synonyms. In cases where a CAS number was lacking, chemicals were identified using three major tools. The primary tool used for chemical identification was HSDB, maintained by the US National Library of Medicine (NLM). HSDB provides a wide range of information, including synonyms, toxicity, and chemical use (NLM, 2008). Next, the Registry of Toxic Effects of Chemical Substances (RTECS) was accessed. RTECS was developed by the US National Institute for Occupational Safety and Health (NIOSH) and contains information on chemical synonyms and primarily mammalian toxicity (NIOSH, 2008). If neither of these databases provided the needed information, an internet search was conducted. Preference was given to scientific and regulatory sources, but it was sometimes necessary to rely on Material Data Safety Sheets (MSDSs) or other business information to obtain a CAS number. Although we were unable to identify a CAS number for all HPC entries (e.g., mixtures or groups of chemicals), these chemicals remained in our database but were assigned lower priority than chemicals with unique CAS numbers.

As presented in Table 2, the HPC list contains 3710 entries with several chemicals appearing on multiple lists. From the 3710 entries, there were 2160 unique listings. Of these unique entries, specific CAS numbers were identified for 2044 chemicals. To evaluate multiple listings, Table 3 presents the number of unique HPCs, as a function of their occurrence in one or more toxicity information sources. Roughly 36% of the chemicals on the HPC list appeared in multiple sources, while approximately 64% appeared in a single source.

5. Sources of exposure information

In addition to HPCs, another set of chemicals was compiled, based on their detection in biomonitoring studies (i.e., human tissues) and their presence in residential exposure media (e.g., indoor air, house dust, drinking water, consumer products). Using these criteria, chemicals with exposure potential were identified by at least one governmental source, judged to be authoritative. This process was supported by peer-reviewed journal articles, published in the scientific literature.

5.1. Biomonitoring studies

Biomonitoring studies report chemicals or their metabolites detected in human tissues (e.g., fat, blood, hair) and fluids (e.g., breast milk, urine). As such, these studies provide direct evidence of environmental chemical exposure. Authoritative sources for our investigation included the National Health and Nutrition Examination Study (NHANES) and the Danish National Birth Cohort (DNBC) study.

NHANES is an ongoing series of surveys designed to collect data on the health and nutritional status of the US population. For each year since 1999, roughly 7000 US residents are interviewed, while approximately 5000 of these individuals provide blood and urine samples for analysis of environmental chemicals (CDC, 2008a). These surveys are statistically designed (i.e., stratified multistage probability sample) to select a representative sample of the civilian non-institutionalized US population, including children. The NHANES study, accessed in our study, was the Third National Report on Human Exposure to Environmental Chemicals (CDC, 2005). We also reviewed biomonitoring articles published after the Third National Report was issued in 2005 (CDC, 2008b).

The objective of the DNBC study in Denmark is to assess how the period from conception to early childhood influences health conditions later in life. Between the years 1997 and 2000, mother and child pairs were recruited into a long-term study to evaluate the impacts of early chemical exposures upon subsequent child development (Olsen et al., 2001). Approximately 60,000 pairs had been recruited by August 2000. A component of this research included obtaining blood samples from both mother and child with follow-up contact after seven years. DNBC results were treated as an authoritative source of chemical exposure information in our study (DNBC, 2008).

Table 3
Number of High Priority Chemicals (HPCs) as a function of number of toxicity information sources.

Number of toxicity information sources	Number of HPCs with unique CAS[a]	Percent of total
1	1318	64.5
2	354	17.3
3	192	9.4
4	68	3.3
5	46	2.3
6	30	1.5
7	19	0.9
8	5	0.2
9	3	0.1
10	6	0.3
11	2	0.1
12	0	0
13	1	0.1
	2044 unique (CAS)	100

[a] CAS = Chemical Abstracts Service registry number.

5.2. Drinking water

Chemicals found in drinking water are a potential source of exposure to children. An authoritative source of chemical data in drinking water is provided by the US EPA Drinking Water Program (USEPA, 2008k). EPA is responsible for evaluating and protecting water quality for US residents and has established concentration limits for contaminants in drinking water (e.g., maximum contaminant levels).

5.3. Indoor air and house dust exposure

Indoor air and house dust are potential chemical sources of exposure to children. These exposure media were treated together, because many studies report results on both media. Authoritative sources of exposure data on indoor air and house dust are the California Air Resources Board (CAARB) (CalEPA, 2008b) and the German Environmental Survey (GerES) (GerES, 2008).

CAARB is part of CalEPA and is responsible for evaluating and protecting air quality for residents of the state. CAARB has conducted research on various aspects of air pollution, including indoor air and house dust (CalEPA, 2008c). GerES is a series of nation-wide surveys conducted to evaluate exposure of the German population to environmental contaminants (GerES, 1998). Approximately 5000 people throughout Germany are included in each GerES, and chemicals in indoor air and house dust are evaluated.

5.4. Consumer products

Often details on chemicals used in consumer products are proprietary, and businesses are reluctant to provide this information. As a result, this information is difficult to obtain. However, the Danish EPA (DEPA) and the Dutch Food and Consumer Product Safety Authority (DFCPSA) have evaluated many consumer products, including those marketed to children. These commodities include baby products, hobby supplies, toys, and child cosmetics (DEPA, 2008; DFCPSA, 2009).

In most of these surveys, DEPA and DFCPSA purchased consumer products from retailers and analyzed these products for chemicals of concern. Resulting reports provide extensive information on chemicals in consumer products and are useful for identifying CHCCs. As

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such, we regard DEPA and DFCPSA as authoritative sources of information on chemicals in consumer products, particularly those marketed to children.

5.5. Support from scientific literature

In order to assess emerging chemicals of concern, sources of exposure information were supplemented with research, published in scientific journals. Initial searches were conducted in databases, maintained by the National Library of Medicine (i.e., PubMed and TOXNET.) However, due to limited information contained in article abstracts and costs associated with full article retrieval, our search focused on the following three journals:

- Environmental Science and Technology (http://pubs.acs.org/search/advanced)
- Environmental Health Perspectives (http://www.ehponline.org/)
- Toxicological Sciences (http://toxsci.oxfordjournals.org/search.dtl).

Other journals were accessed on a limited basis. We intend to broaden our review and add more sources in the future, as time and budgets allow. The addition of more scientific articles would expand the number of chemicals to which children are potentially exposed.

Articles were selected from these journals, using a keyword search that identified terms related to biomonitoring and residential exposure media relevant to children (Table 4). Additional criteria were established to limit and prioritize articles for evaluation. Only the recent literature (i.e., 1994–present) was reviewed to highlight more current methodology. Although most articles described exposures in the developed world (e.g., US, Canada, Europe, Japan), literature on indigenous populations was also included (e.g., Native people of North America and Europe) to address potential transport of environmental chemicals to more remote locations (SETAC, 2008; Scheringer, 2009).

6. Compilation of sources of exposure information

Table 5 identifies the number of chemicals identified from each of the four exposure information sources. Consumer products comprised the largest source, contributing approximately 69% (1798/2607) of the chemicals. Of the total 2607 chemicals, 2219 unique chemicals were identified by CAS numbers. In addition, Table 6 presents the number of unique chemicals (with CAS numbers), as a function of their occurrence in one or more exposure information sources. Approximately 13% of these chemicals appeared in multiple sources, while about 87% appeared in a single source.

A detailed compilation of chemicals relevant to exposure can be found in Table S2, published online as supplementary material (Excel file). Table S2 includes chemical name and CAS number (when available), listed by exposure source. In addition to exposure source information, Table S2 presents a detailed summary of all chemicals with and without CAS numbers, as well as unique chemicals with and without CAS numbers. Each column heading in Table S2 represents a specific literature source that identifies individual chemicals relevant to exposure. Full references for these literature sources are found in Table S4. With this information, the methodology provides transparency on exposure sources employed to identify chemicals.

Table 4
Keywords used in literature search to identify sources of exposure information.

Biomonitoring studies	Indoor air and house dust	Drinking water	Consumer products
Adipose	Indoor air	Drinking water	Consumer products
Biomonitoring	Dust	Public water	Product
Blood	Home	Water	Products
Blood level	House	Water supply	Toys
Breast milk	Indoor		General
Cord blood			Child
Cord serum			Children
Exposure			
Human			
Human exposure			
Infant			
Infant exposure			
Tissue			
Maternal blood			
Placenta			
Urine			

Table 5
Number of chemicals associated with each exposure information source.

Exposure information source	Number of chemicals
Biomonitoring studies	280
Drinking water	239
Indoor air and house dust	290
Consumer products	1798
	2607 total
	2419 unique (sum)
	2219 unique (CAS)[a]

[a] CAS = Chemical Abstracts Service registry number.

7. Identification of CHCCs

CHCCs were defined as those HPCs that were detected in biomonitoring studies or residential exposure media (Fig. 1). We identified 476 CHCCs, as the overlap between our HPC and biomonitoring studies/exposure media lists. A compilation of CHCCs and their CAS numbers can be found in Tables S3A and S3B, published online as supplementary material (Excel files). In particular, Tables S3A and S3B provide details on toxicity and exposure sources, respectively, for CHCCs. These CHCCs have been identified because of the potential risk they pose to children. Further assessment is necessary to prioritize these chemicals, based on the strength and weight of evidence of toxicity and exposure data (Karr, 2009).

Our list of CHCCs was further characterized by evaluating chemical use information to assess potential exposure to children. For those chemicals without a known use, HSDB served as our primary source of information, along with an internet search. Examples of potential use categories are shown in Table 7.

Several limitations hinder identification of emerging chemicals of concern which may become CHCCs. These include incomplete data on toxic effects (e.g., IARC Group 2B describes chemicals as possibly carcinogenic to humans), as well as limited data on early life stage exposure (e.g., data gaps on prenatal and early postnatal exposures). However, as more data become available, these emerging chemicals of concern can be further evaluated with respect to potential CHCC status.

8. Summary and conclusions

As directed by the Children's Safe Product Act (CSPA) in Washington State, we have established a methodology to identify Chemicals of High Concern to Children (CHCCs), using authoritative scientific and

Table 6
Number of chemicals as a function of number of exposure information sources.

Number of exposure information sources	Number of chemicals with unique CAS[a]	Percent of total
1	1928	86.9
2	211	9.5
3	63	2.8
4	17	0.8
	2219 unique (CAS)	100

[a] CAS = Chemical Abstracts Service registry number.

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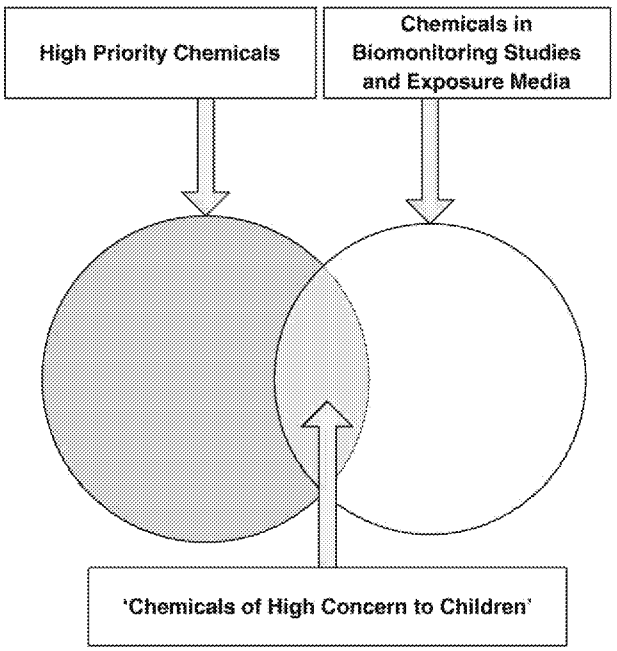

Fig. 1. Identification of Chemicals of High Concern to Children (CHCCs).

government sources of toxicity and exposure information. High priority chemicals (HPCs) with known toxicity were identified, along with chemicals to which children may be exposed. Potential exposure was assessed by chemical detection in human biomonitoring studies and chemical presence in residential exposure media (i.e., indoor air and house dust, drinking water, consumer products).

CHCCs were defined as those HPCs with potential exposure to children. In terms of numbers of chemicals with CAS registry numbers, we identified 2044 HPCs and 2219 chemicals with potential exposure to children, resulting in 476 CHCCs. Further assessment will be conducted to prioritize these chemicals, based on the strength and weight of evidence of toxicity and exposure data.

This process of compiling chemicals of concern represents only an initial step in developing a strategic framework to address chemical contaminants in children. For example, complementary work involves designing both longitudinal and cross sectional studies to evaluate pregnant women, infants, and children to assess chemical exposures at critical windows of vulnerability, along the continuum of human development.

Although our methodology was somewhat constrained by requirements in the CSPA, toxicity and exposure criteria employed were useful for CHCC identification. Our approach for identifying chemicals of concern is flexible to accommodate the dynamic nature of the process, as new data become available, and transparent to allow users to replicate our methods. It is hoped that this methodology may not only guide future regulatory actions but also inform chemical management policies, aimed at protecting children's health.

Table 7
Examples of potential uses for Chemicals of High Concern to Children (CHCCs).

Category	Subcategory
Pharmaceuticals	
Personal care products	Synthetic musks
	Parabens
	Preservatives/surfactants
PBDEs and other flame retardants	
Plastics and plasticizers	Phthalates and other plasticizers
	Plastics, plastic monomers, and plastic related chemicals
	Plastic additives
Pesticides	
Metals, metal containing compounds and element based ions	
Degradation products/contaminants	Dioxins
	Furans
	Polycyclic aromatic hydrocarbons (PAHs)
Solvents	
Halogenated chemicals	Perfluorinated compounds (PFCs)
	Polychlorinated biphenyls (PCBs)
	Chlorinated paraffins
	Other halogenated compounds
Flavoring agents/food additives	Colorants/pigments
	Synthetic flavoring agents
	Additives

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eiar.2009.11.002.

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